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Secção Autónoma das Ciências da Saúde

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O Medical Scientific Liaison numa Unidade de Negócio de Oncologia

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Projeto apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica da Doutora Sandra Margarida Amaral, Responsável dos Assuntos Médicos da Novartis Oncology Portugal e do Professor Doutor Bruno Gago, Professor Auxiliar Convidado da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro.

Dedico este trabalho à minha Mãe, a quem daria uma grande alegria com a conclusão deste mestrado.

o júri

presidente

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palavras-chave Estágio; Indústria Farmacêutica; oncologia; medical scientific liaison;

resumo

A presente monografia expõe algumas das atividades desenvolvidas durante o "in job-rotation" de um ano no departamento médico da Novartis Oncology, como Medical Scientific Liaison, no âmbito do Mestrado em Biomedicina Farmacêutica da Universidade de Aveiro.

Esta monografia descreve a experiência dos primeiros 9 meses, de Março a Dezembro. Muitos foram os desafios e aprendizagens, quer a nível profissional quer a nível pessoal. Apesar de possuir uma experiência de mais de dez anos na Indústria Farmacêutica, centrada nas áreas de vendas e marketing, esta tem sido, de longe, a que mais aprendizagem me proporcionou.

Nos primeiros meses desta experiência, o desafio foi a adaptação de uma nova função dentro da equipa. Concomitantemente, a necessidade de aprofundar os conhecimentos científicos relacionados à área terapêutica dos tumores sólidos, foram também uma prioridade na fase inicial. Foi adquirido um conhecimento essencialmente teórico em várias áreas da empresa, quer a nível nacional, que a nível da sua organização internacional. Sendo uma função relativamente nova na unidade de negócio de Oncologia em Portugal, foi-me dada a oportunidade de conhecer a experiência de outros colegas dentro da companhia que exerceram a mesma função. Assim, as atividades desenvolvidas estenderam-se de contactos com os principais médicos e investigadores em Portugal, a propostas de ensaios clínicos em novas áreas terapêuticas que não eram alvo de foco nesta unidade de negócio.

Nesta monografia são descritos os objetivos do estágio e as atividades desenvolvidas neste âmbito. De seguida, os conhecimentos adquiridos na vertente multidisciplinar do estágio seguidos dos projetos desenvolvidos individualmente. Por fim, apresento uma análise das dificuldades e desafios encontrados bem como os esforços realizados para os ultrapassar.

keywords “On-the-job training”; Pharmaceutical Industry; oncology; medical scientific liaison, medical science liaison

abstract

This monograph sets out the activities performed during the one year 'in-job rotation' as a Medical Scientific Liaison at Novartis Oncology medical department, within the scope of the Pharmaceutical Biomedicine Master's degree course of the University of Aveiro.

This monograph describes the first 9 months from March to December. Many were the challenges and lessons, both professional and personal. Although I already had an experience of more than 10 years working in the Pharmaceutical Industry, mostly in sales and marketing, the present enterprise has been by far the most rewarding.

In the first months of this experience, the challenge was to adapt to a new function within the team. Simultaneously, to deepen my scientific knowledge concerning the solid tumours therapeutic area at this initial stage. I have acquired an essentially theoretical knowledge of some areas of the company's organisation, at national and international level. This being a relatively new function in the Oncology business unit in Portugal, I was given the opportunity to get acquainted with it through the experience of other people inside the company. The activities were from contacts with the main doctors and investigators in Portugal, to proposals for clinical trials in new therapeutic areas, which were not yet targeted by my business unit in the past.

This monograph will describe the goals of the internship and present a description of my main projects. Then the knowledge acquired through the multidisciplinary approach of the internship, followed by the description of each activity. Finally, an analysis of the difficulties and challenges I came across with, as well as the actions taken to overcome them.

Abbreviations List

aBC	Advanced / metastatic Breast Cancer
BD	Business Development
BM	Brand Manager
BTM	Brand Team Meetings
CDA	Confidentiality Disclosure Agreement
CDP	Clinical Development Plan
CEO	Chief Executive Officer
CML	Chronic Mieloid Leukemia
CUP	Compassionate Use Program
CRA	Clinical Research Associate
CRO	Contract Research Organization
Cx	Chemotherapy
EC	European Commission
EFPIA	The European Federation of Pharmaceutical Industries and Associations
EGA	European Generics Medicines Association
EMA	European Medicines Agency
EOP	End-of-Phase
EPAR	European Public Assessment Report
ER	Estrogen Receptor
EU	European Union
FPFV	First Patient First Visit
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GIST	Gastrointestinal Stromal Tumor
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HCP	Healthcare Professional

IND	Investigational New Drug
INFARMED	Portuguese Medicines Agency
INN	International Non-proprietary Name
IIT	Investigator Initiated Trials
KOL	Key Opinion Leader
KPI	Key Performance Indicator
LPLV	Last Patient Last Visit
PAG	Patient Advocacy Group
PgR	Progesterone Receptor
PM	Product Manager
MA	Medical Affairs
MACS	Medical Affairs Concept Sheet
ME	Medical Expert
MSL	Medical Scientific / Science Liaison
MTA	Material Transfer Agreement
NDA	New Drug Application
OAM	Oncology Account Manager
OECD	The Organisation for Economic Co-operation and Development
pNET	Pacreatic Neuroendocrine Tumour
PoC	Proof of concept
Sales Rep	Sales Representative Person
SOP	Standard Operational Procedure

Contents

1. General Introduction

This document reports my in-job Job rotation experience at my current employer company, Novartis Oncology Portugal, as part of the training program of Master's degree in Pharmaceutical Medicine.
It began on the 1st of March 2013 and it was intended to have one-year duration. Herein is the first 9 months experience of a Solid Tumours Medical Scientific Liaison at the Oncology Business Unit, organized as follows:

- Chapter 1: an introduction of the current situation of the Pharmaceutical Industry and the Oncology Business Unit. In addition, chapter 1 describes the evolution of the Oncology Medical Affairs department and the role of Medical Scientific Liaison (MSL). It is also included a brief description about Novartis Oncology as part of Novartis Farma, and my previous professional experience in the Pharmaceutical Industry. Finally, it describes the in-job Rotation main driver and objectives.
- Chapter 2: a detailed approach of activities, projects, knowledge, skills and experience acquired during my training cross functionally.
- Chapter 3: a discussion on the outcomes of the training experience, focused on the accomplishment of goals, expectations, challenges and difficulties.
- Chapter 4: a conclusion with the most relevant learning outcomes of the training experience.

1.1. Pharmaceutical Industry

Global crisis also affected the health sector, and new drugs need to prove cost-effective after careful pharmacoeconomic studies. Although these pharmacoeconomics studies are relatively new, and were created due the global crisis, they are very useful, and tend to be a powerful tool to help payers and prescribes to make decisions. Consequently, the Pharmaceutical Industry is facing the biggest challenge of the last decade. Embedded in a highly competitive market, it has to cope with growing pressures, both from central regulatory approvals, and local

reimbursement agencies. A new chemical entity that has proven (under clinical trial investigation) to have an effective and safe profile by regulatory agencies will not be as easily accessible to patients in need as it was less than 10 years ago. Worldwide, medical prescription of branded medicines is under increasing pressure due to the governmental reduction of health budgets, the loss of major blockbuster patents and also the improvement of generic drug prescription and distribution.
The global financial crisis and subsequent recession, which affected many developed countries, led to austerity policies: governments are introducing a number of cost-reduction strategies, implementing pricing and reimbursement cuts, especially in Europe.

Governments want to save money by introducing different measures like mandatory prescription practices using: the international non-proprietary name (INN), additional charges for medical acts, co-payments by the users of the National Healthcare System, cost-benefit analysis of new drugs through careful pharmacoeconomics studies, implementation of reference pricing in some countries, and promotion of generic drugs uptake. These measures, together with the increasingly tougher regulatory environment, have a negative impact on the pharma industry.
On the other hand, the aging of the world population and consequent increase of chronic diseases like cancer, diabetes and cardiovascular diseases, increase the need for prolonged (sometimes life-long) treatments. Thus, the increasing demand on National Health Services will probably ensure the sector's continuity, even when contained by cost-reductions from the paying entities.

The European Generic Medicines Association (EGA) estimated that the introduction of generic medicines led to savings of €30 billion per year [(1)]. Moreover, in the medium-long term, the market for biosimilars has a very large potential for growth, producing current savings of €1.4 billion in Europe, according to EGA. The European market is considered the leader in the market penetration of biosimilars as far as the regulatory approval pathway for biosimilar drugs is concerned. [(1)]

In response to rising healthcare expenditure, governments in developed markets are looking to encourage generic uptake in order to contain costs. The continuity of the use of the prescription by the INN, in addition to the substitution of the medicine in the pharmacy and pharmacist incentives, are driving generic uptake. The use of reference pricing as observed in Germany further drives the generic drug support, with patent brands facing generic competition from generic versions of me-too drugs. A reference pricing system establishes a reimbursement level (or reference price) for a group of interchangeable medicines. In Germany, the reference price is calculated as a function of medicine prices and the number of generics competitors. Higher reference prices are awarded in reference groups with fewer generics competitors, thereby stimulating market entry of generic medicines companies. Conversely, reference prices are reduced and price competition is stimulated in established markets, but not to the extent that it becomes economically unviable for generic medicines companies to remain on the market.[2]

Approval of complex generics such as Sandoz/Momenta's generic version of Lovenox (enoxaparin sodium; Sanofi-Aventis) is also a significant advance. Complex generic drugs can be divided into four categories:

- Complex Active Ingredients: Low Molecular weight Heparin (LMWH), peptides, complex mixtures, natural source products
- Complex Formulations: Liposomes, iron colloids
- Complex Route of Delivery: Locally acting drugs
- Complex Drug-Device Combinations: Dry powder inhalers (DPI), metered-dose inhaler (MDI), nasal spray, transdermal system [3]

The generics market and the pressure it exerts to revoke major blockbuster patents adds another pressure point to scientific investigation and company pipelines. Although there is a big increase in the production of new chemical entities and in biomedical engineering breakthroughs, the failure rate in the more advanced phases of clinical investigation is still high. This might lead clinical investigation to lose cost-effectiveness, with high levels of investment lacking the expected return.

It is thus imperative for companies that want to deliver innovation in a wide pipeline to enhance the efficiency of drug development.

A continuous body of evidence suggests that the traditional clinical research model is falling into disuse. The basic investigation type, with the subsequent and tightly defined pre-clinical phase and clinical phases 1, 2 and 3, tends to come to an end. The classical clinical phases are as follow:

- Phase 1: safety studies, enrolling 20 to 100 patients or volunteers, to determine the safety in humans and the dosage interval to be used in the other phases. In oncology, the observation of the activity of the compound is also an objective, since the tests are carried out on patients. Phase I trials enrol small numbers of individuals who have advanced stage cancer not amenable to be treated effectively with standard treatments or for which no standard treatment exists.
- Phase 2: the goal is to explore the clinical activity of the medicine and observe the main side effects detected at this phase. Depending on the therapeutic area, 100 to 500 patients are enrolled.
- Phase 3: This is the longest experimental period, since it aims at obtaining efficacy and safety data in order to evaluate the benefit for the patient and the outcome compared to standard treatment. These trials are normally multicentric, randomized, double blind and double controlled (placebo or active compound).

The global drug development process takes 10 to 15 years, and only one in six molecules tested in clinical trials successfully reaches the end of phase 3 and receives the marketing authorization from the regulatory agencies.

Figure 1. The Research and Development Process(4)

This means that, at this moment, biopharmaceutical investigation is slow, risky and not very effective. This sequential and static model, which also has gaps, tends to be replaced by more flexible models that are able to maximize the use of previously acquired knowledge. The phases are then designed as exploratory and confirmatory.

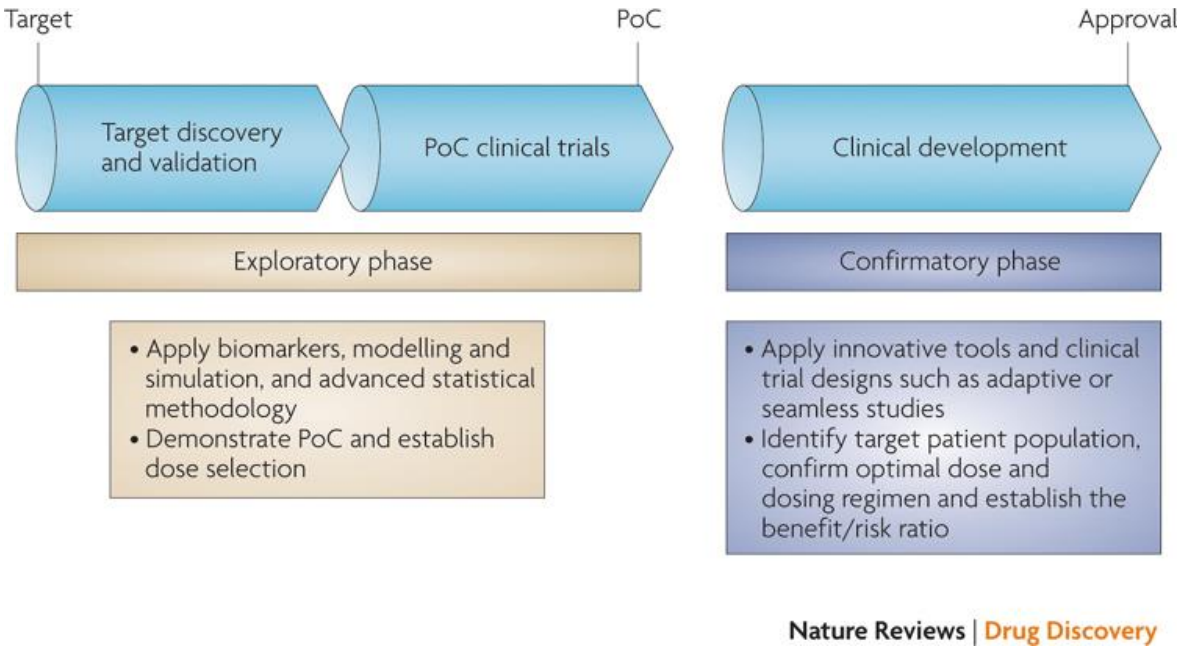


Figure 2. A novel model for clinical development.(5)

During the exploratory phase of development, this model uses all available knowledge and tools, including biomarkers, modelling and simulation, as well as advanced statistical methodology. Trials are designed to determine proof-of-concept (PoC) and to establish dose selection to a level of rigor that will enhance the likelihood of success in the confirmatory phase.

During the confirmatory phase, modern designs, tools and knowledge are applied to larger-scale studies with the goal of: identifying the target patient population in which the drug is efficacious, establishing the benefit/risk ratio, and confirming the optimal dose and dosing regimen. At this phase, innovative clinical trial designs (such as adaptive or seamless studies) compress timelines, improve dose and regimen

selection, and reduce the number of patients assigned to non-viable dosing regimens.[6]

In 2010 the research-based Pharmaceutical Industry invested an estimated € 27,000 million in R&D in Europe. It directly employs 640,000 people and generates three to four times more employment indirectly—upstream and downstream—than it does directly. However, the sector faces real challenges. Besides the additional regulatory hurdles and escalating R&D costs, the sector has been severely hit by the impact of fiscal austerity measures introduced by governments across much of Europe in 2010 and in 2011.(7)

The industry is implementing a number of strategies to drive sales and profitability forward: product innovation, diversification, and cost-containment.

1.1.1. Oncology Business

"All who drink of this remedy recover in a short time,
except those whom it does not help, who all die.
Therefore, it is obvious that is effective in all but the incurable."
GALEN

The treatment of oncologic diseases has undergone some changes in the last few years. Surgery is the most effective alternative to most early diagnosed tumors. However, for more advanced stages, it is necessary to use a systemic approach that aims to eradicate the patient's tumour cells, with or without disease control. This treatment, defined as systemic therapy, may be used alone or in combination with various drugs, according to the situation.

This widely known approach, has demonstrated different results depending on the type of cancer, and is often associated with safety related inconveniences. Specifically, adverse events like alopecia, fatigue, diarrhea or infections, have a major impact on the daily life of patients. It is known that tumour cells prevail over other cells due to their resistance to programmed cellular death, derived from oncogenetic mutations and loss of tumour suppression genes.

Most chemotherapies act upon some stage of the cell cycle, thus we understand that most of the adverse events reveal themselves through rapid growth cells, like gastrointestinal, hair or skin cells.

Also, most chemotherapy is myelotoxic, which means that it also affects the cell of the bone marrow, contributing for the main hematologic adverse events.

However, even with this degree of efficacy, chemotherapy has not proven itself sufficient, mainly because cancer cells may prevail and return, and also due to the hardship and toxicity that patients must endure.

Actually, as I mentioned before, the most advanced cases are rarely cured, especially when metastases are present. Although metastization is a process with a superlative clinical and biological relevance, it is still far from being completely understood. The metastatic process has a number of phases that have to be accomplished in a specific order to originate a metastatic tumor. It is a silent process, so it is extremely difficult to observe.(8)

There was the necessity to take a more profound look into the cell pathways in order to understand how tumour cells resist to cytotoxic therapy creating mechanisms of resistance and disease persistence. One of the most interesting challenges in Oncology is to identify the main path that drives the disease, being at the same time a targetable one.

The evolution of biotechnological sciences and also of the technical capacities of laboratories and equipment, contributed for major advances towards customized medicine. Other players were found in chemotherapy resistance, as well as other factors responsible for the occurrence of the disease. One of the first examples of that major advance is undoubtedly, Chronic Mieloid Leukemia (CML).

ln 1960, P.C. Nowell and D.A. Hungerford, from University of Pennsylvania, isolated the fusion chromosome responsible for CML, which led to the first association between a chromosome aberration and an oncologic disease. That fusion gene is the result of the translocation between chromosomes 9 and 22, as discovered 13 years later by the American geneticist Janet Rowley. The proto-oncogene Abelson (*abl)* is translocated from chromosome 9 into the breaking point of chromosome 22 (*bcr)*, leading to a new protein product with high tyrosine kinase activity and cell proliferation capability.

The discovery that some tumours are targetable, i.e. that express at least a target that can be used to direct specific therapeutics, has completely changed the paradigm of treatment of some diseases and of scientific investigation.

Some 20 years later, the company Ciba-Geigy (currently Novartis) was at the peak of the development of molecules that inhibited molecular targets, called kinases. Kinases act as molecular master-switches in cells—turning "on" some pathways and turning "off" others—thus providing the cell with a coordinated set of internal signals to grow, shrink, move, stop, or die. The human genome has about 500 kinases of which, about 90 belong to the subclass that contains src and Bcr-abl. Each kinase attaches phosphate tags to a unique set of proteins in the cell.[9]

This led to the discovery and investigation of the STI571 molecule, that later become known as Imatinib (Glivec®), "the magic bullet" that drastically changed the life of thousands of CML patients.

The success of Imatinib in the treatment of CML had such an impact that it revolutionized the way new molecules were investigated. This success was only possible due to the concomitant advances in areas like molecular biology, Polymerase Chain Reaction (PCR) technology and sequencing, structural biology, and other related areas of science.[10]

Nowadays, hemato-oncologic therapy has a widespread number of different targetable molecules, supporting the development of drugs such as tyrosine kinase inhibitors and monoclonal antibodies.

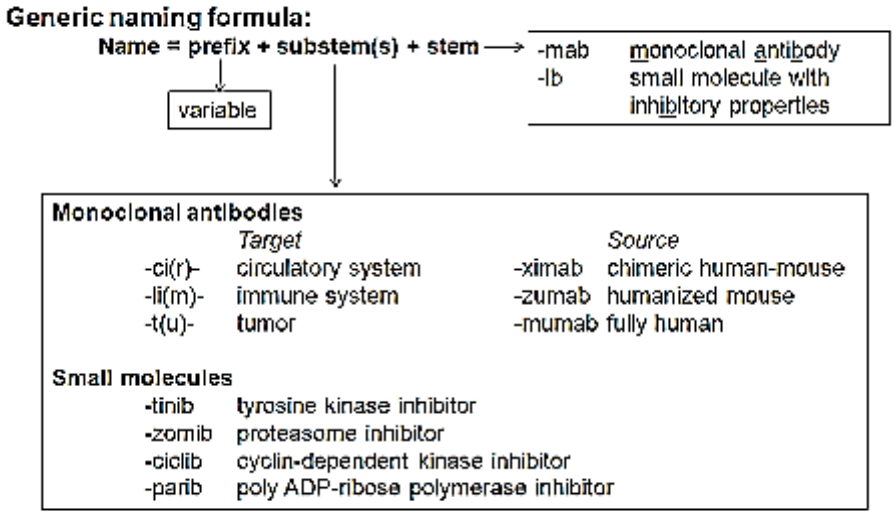


Figure 3. – How the new target therapies are named (8)

Given the specificity and complexity of this type of target therapies, an increase on the cost of treatments is foreseeable. These are highly specific drugs that will only benefit a limited number of individuals. Consequently, the use of generic and biosimilar drugs in oncology has increased in order to accommodate for innovative customized medicine therapies.

Controversially, at the moment, despite the exciting expectations for drug development, there is a clear decrease in new approved medicines, due to cost-reduction policies.

1.1.2. Medical Affairs Department

The designation of *Medical Affairs* department is relatively recent. It was created from the growing need to leverage medical communication in the Pharmaceutical Industry, and has undergone many changes since then. From the smallest biotechnology company to the largest multinational, it is a competency going through a profound transformation, with an increasingly more active role in business and marketing decisions. In fact, the increasing complexity of medicines and drug approval regulations led companies to develop the Medical Affairs strategies—to increase productivity and quality of the results produced.

The Medical Affairs in the Pharmaceutical Industry aims to develop clinical investigation through the local implementation of meaningful clinical trials, as well as through the support to local investigator initiated trials (ITT). In addition, Medical Affairs are responsible to disclose accurate medical information of both unapproved and already approved medicines. One of the ways to communicate about innovative treatments is through interaction with health professionals, not only discussing and informing about therapeutic solutions already commercialized by the company but also engaging medical experts in the active participation in clinical investigation and early access to new therapeutic options.

Specifically, it is important to mention the communication with health professionals in the scope of the experts' dedicated therapeutic areas namely: discussion of recent published data in a given disease area (whether from the company or from the competition) and the response to unsolicited requests which includes the off-label usage of a certain medicine; the communication and report of safety events and pharmacovigilance registries; the coordination and support to investigators scientific publications and clinical trials conduction; and detailed drug information.

Medical Affairs are also responsible for the evaluation, negotiation with the headquarters and management of funds destined to IIT. In the same way,

participation in international multicentre clinical trials, from phase 1 to phase 3, expanded access programs (phase IIIb) or registry studies, are also evaluated and managed by the Medical Affairs Department.
In parallel, training of marketing and sales teams´ medical subjects and disease indications of medicines is also supported by the Medical Affairs Department and may be performed by the Medical Affairs head / director or by the medical advisor.
It is noteworthy to mention that Medical Affairs professionals have advanced degrees that enable them to understand and effectively communicate the science behind a device or pharmaceutical product. Medical Affairs directors are commonly doctors of medicine (MDs or PhDs) and Medical Affairs departments typically have MSLs who have advanced masters degrees, Pharm Ds, or MDs to enable them to interact with physicians and Healthcare Professional (HCP).(11)

A few years ago, the medical department was looked at as a supportive department of marketing and business. Associated competences for clinical trials development, scientific training and clinical sessions were considered necessary for initiating, developing and sustaining the life cycle of drugs. Nowadays, Medical Affairs are deeply involved in the marketing and strategic decisions for drug development and disease indication, in the environment of local therapeutic algorithm and patient unmet needs. Hence, it becomes crucial for any drug launch, that scientific accuracy and robust clinical data can be disclosed and discussed by medical experts in a peer-to-peer perspective. Consequently, companies realized Medical Affairs as a potential asset to increase sales, due to its image of impartiality and scientific rigour and also to the clinical trials, supporting the high level mission of giving patients access to innovative medicines.
All these activities must be based on great legal and ethical rigour, so as not to interfere with Medical Affairs trustworthiness, and in a long run with the compliance integrity of the company. Medical Affairs integrate different role profiles, namely medical advisors, clinical research associates, medical scientific liaisons, and different levels of management of groups of the referred roles, that ultimately report to the medical director.

Frequently, all functions are comprised in a single department. Some companies outsource clinical investigation management services to clinical research organizations (CRO). [12]

1.1.3. Medical Scientific/ Science Liaison (MSL)

MSLs are field-based scientifically qualified professionals that provide non-promotional medical support to ensure the safe and effective usage of the compounds or medical devices, in scientific partnerships from Phase II until commercialisation with HCP, clinical investigators, and key decision makers through effective scientific interactions.

MSLs build and develop advocacy on a peer-to-peer level through the disclosure and discussion of scientific and clinical data in a non-promotional activity. MSLs should at all times reflect the medical nature of their role, be fair, balanced, non-promotional, and scientific and evidence-based. MSLs must ensure full compliance with standard operating procedures (SOPs) and local laws and regulations for all medical and promotional activities.

MSLs prepare and support the development, launch and commercialization of drugs through medical education and relationship management of medical experts (MEs) and key opinion leaders (KOLs). While exchanging scientific data, the MSL can share Investigators' recommendations and seek for research proposals that are consistent with the product development strategies, hence facilitating IIT development. MSLs play a critical role in the scientific exchange with opinion leaders in the medical community.

Because of the field based facet of MSLs, they can provide support to clinical development colleagues in site selection and to investigators conducting clinical trials.

The MSL must be a highly trained professional, with a deep understanding of the scientific background involving the medicine and a good knowledge of the disease for which the drug is indicated to treat. That is of utmost importance, as the MSL needs to be seen as a peer or highly knowledgeable in the field, to be able to provide technical and clinical information concerning disease treatment options and pipeline. That also

means to be able to discuss different treatment options that lie beyond the company's own proposals, having an overview of the overall management of the disease. This knowledge will also empower the MSL to discuss potential research opportunities with investigators.

Through their expertise and external interactions, MSLs can gain insights which will assist in the development and execution of innovative strategies and plans that clearly support development of strategies and actions to leverage the company results.

The profile of a MSL must include communication skills, both oral and written, to interact with KOLs and ME, in face-to-face meetings or in public talks. In that area, soft skills and self-confidence are closely related.

As a consequence of the new regulatory guidelines and limited access to the HCP, the role of the MSL has gained more importance. As a consequence, the field sales representative role tends to contract and to be replaced by Key Account Managers.

Based on my experience and on discussions with other MSLs, also from other countries, the path to articulate coordination between MSLs and Sales Rep is still under development, as colleagues share the same customers in the same company but communicate different contents from diverse subjects.

It is very important to comply with the rules of communication for developing products and unsolicited questions, so that they are not perceived as commercial communication.
In order to ensure that MSLs maintain their status of medical/scientific role based on a non-promotional communication, companies had to set policies to clearly isolate them from promotional sales roles. Consequently, MSLs are increasingly having their own space to communicate, that should not be the same of sales representatives according to what has been published to this date. [13]

The current policies aim to defend the integrity of the MSL role within the Medical Affairs goal. However, in this fast changing environment, many of the pharmaceutical company's employees, namely sales roles, are still not prepared for the fast change in status. Hence, often they interpret the separation of roles/status as a depreciation of their work. In this context, MSLs have an extra challenge to face, which is to articulate with marketing and sales colleagues in a productive way with mutual support and respect, albeit the necessary limitative measures. On the other hand, since MSLs and sales force are field-based functions and have interactions with common stakeholders, namely KOLs and some MEs, it is important that the contents of communication from the two different roles reach the stakeholder in a complementary way and are not perceived as unfocused and disorganized communication.

One of the most important goals is to clarify where the role of the MSLs differs from the sales representative, particularly in specific and technical areas as Oncology. In fact, the sales force in Oncology is perceived as highly scientifically trained; however, they cannot discuss off-label medicines, non-approved drugs of the pipeline, or educate about the disease area. This should be clearly the focus of the MSL activity. However, the companies have already made an effort and took some measures in that direction, such as applying specific Key Performance Indicators (KPI) to MSLs that are clearly different from Sales and Marketing colleagues. One example is that there should be no sales objective behind the MSL activity.

The metrics should be concrete and reachable goals that apply to each MSL's activities. The report from Cutting Edge Information titled "How to Compensate a Winning MSL Team" discuss some of the metrics used to measure MSL performance, as:

- Number of IITs submitted
- Number of KOLs visited
- Age and depth of relationship with KOLs
- Number of articles/publications authored
- Number of scientific/educational speeches delivered
- Customer feedback

The MSL role still has to undergo many developments, particularly in Portugal and in the Oncology area. From communication models to specific working areas (development vs. approved medicines), the field of operations of an MSL is still not totally clear.

I feel that it is extremely important to be a part in what may be the building of a better path for the MSL career, contributing to a clearer definition of the main goals and tasks, and to withdraw from it a real benefit for the scientific community and, most importantly, for the patients.

1.2. Novartis Farma and Novartis Oncology

The Novartis Farma Group is one of the top five pharmaceutical companies in the world. It has several business units (ranging from veterinary to the investigation of diagnostic devices):

- Pharmaceuticals: innovative patent-protected medicines
- Alcon: global leader in eye care with surgical, ophthalmology and consumer products
- Sandoz: affordable, high-quality generic medicines and biosimilars
- Consumer Health: self-medication products and treatments for animals
- Vaccines and Diagnostics: vaccines and diagnostic tools to protect against life-threatening diseases

Novartis mission is to discover, develop and successfully market innovative products to prevent and cure diseases, to ease suffering and to enhance the quality of life. [14] Present in more than 140 countries and with more than 125,000 associates worldwide, Novartis is the result of the merger of Ciba-Geigy and Sandoz, two companies with a rich and diverse corporate history. Throughout the years, Novartis and its predecessor companies have discovered and developed many innovative products for patients and consumers worldwide. [14]

Novartis Oncology

The oncology community shares a common mission: to transform the way patients live with cancer and related diseases. Novartis Oncology's focus is on the discovery and development of innovative medicines, but also on the effort to make them accessible to our patients.

With nearly 7,000 employees operating in 55 countries, Novartis Oncology has a truly global reach. It has the advantage of talented and globally diverse employees who, through shared goals and different perspectives, are dedicated to transforming the lives of patients living with cancer around the world. Novartis Oncology has developed five new practice-changing medicines in the past decade (bisphosphonates, imatinib, nilotinib, ruxolitinib and everolimus) addressing unmet medical needs in patients worldwide. Our broad pipeline includes 12 new molecular entities in development and 15 new indications, targeting key molecular pathways in cancer biology for the next five years.

Open partnerships within the oncology community enable the company to realize the power of collaboration, leading to the development of breakthrough therapies that impact on patients' lives, as follows:

- Relationships within the oncology care community enable the company to conduct high-quality clinical trials with competitive timelines and aid in the discovery and development of new medicines and indications to benefit patients.
- Patient groups and advocates provide a better understanding of patient needs and barriers to the success of treatments.
- Health authorities help us to speed delivery of new treatments for patients through ongoing dialogue and innovative approaches to regulatory review and approval.
- Biotech partners complement our research and development strategy, from basic research through commercialization.

- Payers help us improve availability of new therapies to patients most likely to achieve results(15)

Novartis Oncology believes that a company can only aim to achieve its mission towards the commitment to patient care, once it is open to the environmental changes and flexible enough to adjust internally in order to deliver externally.

At Novartis Oncology, research is driven by a distinctive scientific and clinical strategy, focusing on unmet medical needs and knowing disease pathways. The company's targeted research strategy leverages biomarkers and targeted drug development focused on personalized medicine. In addition, many rare disease indications are launched and developed, because Novartis Oncology believes that *no patient should be left behind.*

The company's approach speeds the availability of targeted treatments through:

- Enhanced screening and identification of promising compounds and combinations.
- Better patient selection and outcome prediction biomarkers to increase likelihood of success.
- Delivery of targeted treatments with companion diagnostics to optimize patient outcomes.

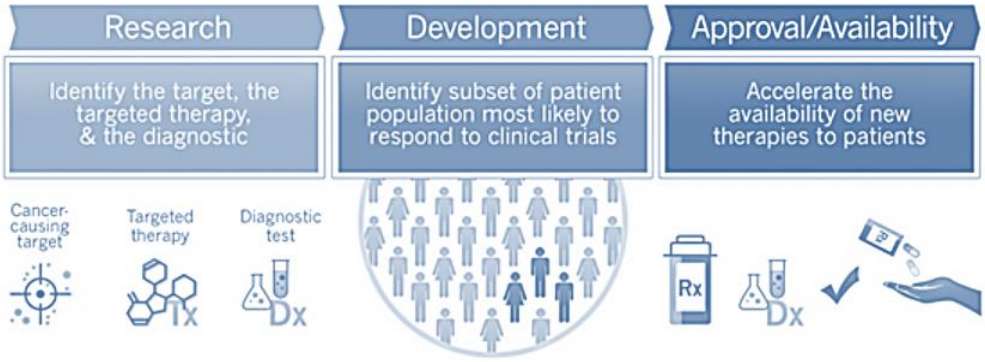


Figure 4 – The Novartis Oncology Research Model(15)

Since Novartis Oncology is a company oriented for the patients, the future and technology, it is an ideal company to be at the forefront of the communication and

utilization of this new resource (MSLs) to share its mission with the main MEs and KOLs.

1.2.1. "In-the-job rotation" objectives

The job rotation programme allows the organization to dispose of a selection of personnel with the capacity to hold key positions, which has the required training and is able to change roles rapidly.

Objectives of the Job Rotation(16):

- Reducing the monotony of job
- Sucession Planning
- Creating Right Employee-Job Fit
- Exposing associates to other roles within the company
- Testing Employee Skills and Competences
- Developing a Wider Range of Work Experience

By performing a job rotation, associates are equipped with the tools necessary to carry out the new job and, simultaneously, acquire key contacts with internal roles at the international company structure.
This opportunity has been used by a large number of companies both in the USA and in the OECD (The Organisation for Economic Co-operation and Development). countries for the last 20 years. The number of key employees that have been involved in rotation experiences has increased in the last years, as P. Osterman analysed in his work: "Work reorganization in an era of restructuring: Trends in diffusion and effects on employee welfare." (17)
Experts in this area argue that this is a beneficial strategy that captures the associate's learning attention and also increases the human resources capital while promoting professional development.
These are two theories, Learning and Motivation, which emphasize the effects of Job Rotation in the work of a collaborator. Others suggest that the rotation (18)

Figure 5: Talent Development impact: Cross functional rotation has the most significant impact on talent development among all programs

1.3 Previous role in Novartis Oncology

I have been working in the Pharmaceutical Industry for about 15 years.

I started my professional career in a very small company dedicated to commercialize contact lenses. My job was to sell the lenses in optical centres and to promote their use by ophthalmologists. This experience lasted about one year, since I soon realized that there were other opportunities in the Pharmaceutical Industry by working specifically with medicines instead of medical devices.

After that experience I truly embarked in the pharmaceutical industry, starting to work at Rhône-Poulenc Rorer. I was responsible for an antibiotic designed for hospital use and a low molecular weight heparin for the prevention of deep venous thrombosis and treatment of Non-Q-Wave Myocardial Infarction. That is how I initiated my experience in the Pharmaceutical Industry and had my first contact with oncology. It was then clear to me that it was an area I would certainly like to work in.

I reached that goal when I joined the hematology team at Roche, with a product for the non-Hodgkin lymphoma. The product was rituximab, one of the first monoclonal antibodies used in the treatment of a hemato-oncologic disease. This experience was extremely important to my professional career, because I did confirm that oncology was the area I wanted to work in, particularly with innovative drugs.

Still at Roche I had the opportunity to work in the marketing department, being responsible for trastuzumab as Product Manager (PM), a drug used in a specific type of breast cancer that has an overexpression of HER2 (Human Epidermal Growth Factor – 2).

The marketing experience taught me a great deal about interpersonal relations within a company. At that time, to become a PM demanded from me leadership skills that I still had not developed. I realized that it is extremely challenging to defend and argue about the pertinence of our ideas with others in the team, as the challenge is to create a common view. More than competence and knowledge, to truly achieve team work one needs to build trust, leadership, charisma, and respect. Without that, the work of a PM is extremely slow and difficult.

Another disappointing aspect at the time was the heavy load of internal meetings and, consequently, the loss of contact with the external clients. Apart from that, my belief that I wanted to work with innovative products was strengthened. And it was very enriching to get acquainted with the international part of the company and get to know how processes and decisions were made. So I ended my marketing experience and decided to return to a field-based position, still in research.

So, I started working at Jansen-Cilag, where I was responsible for the commercialization of bortezomib, a novel first-in-class proteasome inhibitor, a major breakthrough in the treatment of multiple myeloma.

In 2006, I joined Novartis, and accepted the challenge of being responsible for imatinib in Lisbon's main centres. I have worked both indications, gastrointestinal stromal tumours (GIST) and CML.

Knowing about the significant market changes, my intention to embrace a different kind of project increased, namely in the medical area. Since I always wanted to develop my scientific knowledge, I began gaining competences and aiming at a position as MSL.

With that in mind, I applied for the Master's degree in Pharmaceutical Medicine, in order to acquire other competences that, together with my experience in sales and marketing, could lead to a successful career in the medical department.

Pharmaceutical Medicine is the medical scientific discipline related with the discovery, development, evaluation, registration, monitoring and medical aspects of the marketing of medicines for the benefit of patients and the health of the community. In this rapidly expanding field of medicine there is a need for high quality education programmes that are compliant with the PharmaTrain initiative of the Innovative Medicine , but also with the Bologna process.

The main objective of the PharmaTrain project is to build and implement a new modular Master level programme for advanced studies in Pharmaceutical Medicine and Drug Development Sciences. The programme is based on the Bologna credit and title system and builds on the new PharmaTrain Syllabus 2010 of the European Federation of Courses in Pharmaceutical Medicine (EFCPM). PharmaTrain is funded by the Innovative Medicines Initiative (IMI) Joint Undertaking.

In the following paragraphs I will make a brief description of the programme in Pharmaceutical Medicine, as I believe that it is very important to state that it was very useful for the knowledge I have acquired.

The "Training Programme in Pharmaceutical Medicine" at the University of Aveiro, has been established since 2010 as an initiative of a group of experts from the academia, regulatory bodies, clinical research sites and pharmaceutical companies that identified a need for continuing education and qualification of pharmaceutical medicine professionals.

The programme is extremely flexible, with 3 days of required in-person classes in approximately a month. The location of the modules has alternated between the locations in Lisboa and Aveiro. The remaining activities were carried out via e-learning. Only in this manner was I able to participate in a course of such complexity and located in Aveiro.
The programme has the support and collaboration of the Association of the Portuguese Pharmaceutical Physicians (AMPIF) and the Portuguese Medicines Agency (INFARMED).

The Master´s degree in Pharmaceutical Biomedicine is obtained after the conclusion of nine required curricular units, four optional units and a thesis. The whole programme is in compliance with the PharmaTrain syllabus.
The programme´s mission is to train new people that are capable to work in a company's medical departments, in investigation units or regulatory agencies.
It gives the students a vast perspective of what the life cycle of a pharmaceutical compound is, providing them with the required competences to work at the level of development stages and regulatory processes. In my case, I attended the following required curricular units:

- Introductory Module: Product Research and Development Process: Outline and critically appraise the principal steps in drug discovery, explain the rationale for the complete development plan (pharmaceutical, pre-clinical and clinical) according to the proposed therapeutic indication;
- Non-Clinical Testing, Pharmaceutical & Early Clinical Development: From Drug Discovery to First in Humans
- Exploratory & Confirmatory Clinical Development: Clinical Pharmacology
- Clinical Trials: Clinical Development: Demonstrate competence in the management of all life-cycle activities (regulatory and marketing) of a medicine.
- Regulatory Affairs, Drug Safety & Pharmacovigilance I: Medicines Regulation / Regulatory Affairs: Critically review the issues (including legal, ethical and clinical) involved in the undertaking of clinical research Appraise and compare the regulation of medicines in the various global markets
- Regulatory Affairs, Drug Safety & Pharmacovigilance II: Drug Safety And Pharmacovigilance: Assess and compare the management of drug safety issues pre- and post-marketing authorisation, Develop and critically appraise product-related information to ensure adherence to ethical and legal provisions
- Systematic Review and Meta-Analysis: Clinical Data Management And Analysis

- Healthcare Marketplace & Economics of Healthcare: Explain the principles of health economics and discuss their application in the development and marketing of medicines
- Clinical data Management and Analysis: Critically review and interpret the literature relating to drug research and usage

And the following optional units:

- Project management: Define a project; define differences in organizational structures as well as their impact on leading a clinical development project. Review the Project Management Body of Knowledge (PMBOK) framework
- Medical Affairs: Know the roles and responsibilities of the Medical Affairs and main trends regarding organizational structures within the pharmaceutical industry.
- Medical Writing and Communication: to acquire the basic principles of the scientific writing, to present study data.
- Translational Medicine: Understand the concept of translational medicine, the current challenges in translational science and its research pathways. Understand how cellular products, pharmacogenetics, biobanks, experimental surgery and medical engineering can lead to target identification. Know what a biomarker is and their different classes
- Statistics Applied to Clinical Research: Explore data analytically and graphically. Analyse results from different ANOVA types: between subjects factorial experiments; within-subjects experiments; mixed factorial experiments; post-hoc multiple comparison tests; non-parametric ANOVA tests. Explore survival analysis results: Survival functions; comparison of clinical life tables and Kaplan-Meier method. Power analysis and sample size estimation. [19]

The training provided by the Master's Degree allowed me to develop the competences and skills necessary to apply for a new role inside the organization, as a MSL in the medical department.

One of the major premises of Novartis philosophy is the people. So, Novartis associates can apply for a "Job Rotation", which means an *in-job* training, in an area that is the aim of a career development plan. When I started the Master's Program, I have informed my manager about my desire to start an internship in the medical department.

2. The Medical Science Liaison Experience

As I stated before, one of Novartis' priorities is the training of its associates, whether by granting scholarships or encouraging the search of knowledge in areas that may be fundamental for the company.
Such is the case of the in in–job Rotation program, aiming to provide field experience in the area that the candidate wants to develop. It is almost like an internship. Since I have demonstrated my wish to collaborate with the medical department and I am attending this master's degree, I have been given the opportunity to do a one year job rotation as a MSL in the solid tumours area at a national level.
I am currently responsible for the field based medical communication for breast cancer, renal cell cancer, pancreatic neuroendocrine tumours, melanoma and lung cancer. One of the medicines is already on the market, with a co-payment pending, and the others are still at an investigation stage.
In this chapter I will then enumerate the therapeutic areas I have been involved with, as well as other activities that I have carried out during these nine months, both at an interdepartmental level and individually.

2.1 Therapeutic Areas

Novartis Oncology has many therapeutical areas, from hematologic tumours, endocrine tumours and solid tumours. Here I will describe the main therapeutical areas that I have worked on.

2.1.1 Advanced Breast Cancer (aBC)

Breast cancer is still the main worldwide cause of death for women and is by far the most common form of cancer diagnosed in European women, accounting for 29% of total cases of cancer diagnostics. [20]
Nowadays, due to the therapeutic advances, many women are able to live several years with the disease: surgically cured or therapeutically controlled.

This progress has been very slow. The first major breakthrough in breast cancer treatment is slightly older than a hundred years, when the hormonal dependence of breast cancer was discovered.

Around 1890, George Beatson, an English Surgeon trying to improve his surgical techniques, studied a group of sheep with advanced breast cancer. He observed that the tumour shrank for those that had been oophorectomized. That observation led him to surgically remove the ovaries of three patients with advanced breast cancer and study the outcome. As he had anticipated, a clear improvement of the disease occurred and the tumours shrank impressively. This finding was then replicated in London by others surgeons in a larger group of patients and the findings were similar, but only in two-thirds of the breast cancer patients. A cause-effect relationship was thus established for the first time in an oncologic disease.

However, the discovery of estrogens was made several years later by Edward Doisy, in 1929. Later, it was discovered that the ovaries are responsible for the production of estrogens, which in turn are responsible for about 70% of all breast cancers.

Around 1960, with the discovery boom of laboratorial and chemical substances, there was a rush in search of substances to promote birth control. This led to the discovery of a molecule, ICI4647, which seemed to fulfil that goal. But the result was the exact opposite, since it produced a blockage in the estrogens chain, shutting off the estrogens' signal in many tissues. It was an estrogen antagonist and the investigation was abandoned, since it was considered a useless compound.

Mary Cole, an oncologist and radiotherapist with a special interest in breast cancer, realized how much potential the abandoned drug had. She started a clinical trial involving 46 women with advanced or metastatic breast cancer who were treated with the ICI4647 tablets. The response shown in 10 patients contributed to one of the major breakthroughs in oncology. That abandoned drug was tamoxifen, which was—almost by accident—the first target therapy used in oncology.

M. P. COLE, C. T. A. JONES AND I. D. H. TODD
From the Christie Hospital and Holt Radium Institute, Manchester M20 9BX

Received for publication April 7, 1971

SUMMARY.—An introductory clinical trial of the anti-oestrogenic agent ICI46474 in late or recurrent carcinoma of the breast is described.

Forty-six patients have been treated, of whom 10 have shown a good response. This is of the same order as that seen with oestrogens and androgens.

The particular advantage of this drug is the low incidence of troublesome side effects.

Figure 6: The abstract of Dr. Mary Cole paper about the first clinical trial with tamoxifeno

During 1970-1980, the emergence of new technologies led to an evolution of the strategies to treat, diagnose and stage the breast cancer.
According to our current knowledge, one may classify breast cancer into five different groups:

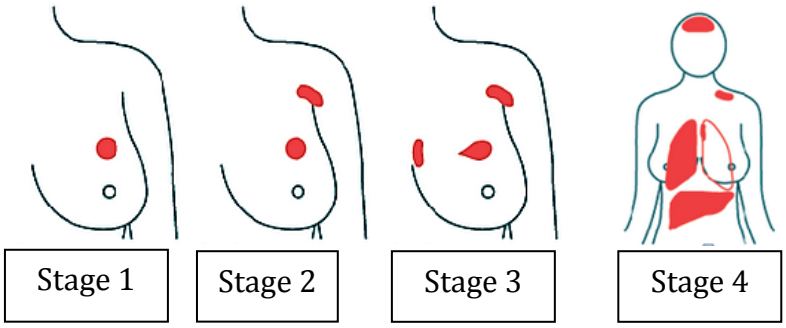
- Luminal A – estrogen receptor (ER) and /or progesterone receptor (PgR) positive, HER2 negative and Ki-67 low (<14%)
- Luminal B /HER2 negative - ER and /or PgR positive, HER2 negative and high Ki-67
- Luminal B /HER2 positive - ER and /or PgR positive, HER2 positive, any Ki-67
- Erb-B2 overexpression - HER2 Positive (non-luminal) – HER2 overexpresses or amplified, ER and PgR absent
- "Basal-Like" - Triple Negative – ER and PgR absent, HER2 negative

And as far as therapeutic strategy is concerned, the treatment strategy for a patient should be discussed in a multidisciplinary team meeting of several professionals with an expertise and knowledge in Breast cancer such as:

- Pathologist
- General / Reconstructive Surgeons
- Medical Oncologist
- Radiation Oncology
- Nursing Experts

The discussion and decision making aims mainly at one of two basics situations: curable approach or palliative care. The direction and the sequence of the treatment are dependent of the clinical and pathological stage of the tumour, the subtype of the tumour and the biological characteristics of the tumour.

Figure 7: Breast Cancer Stages



Stage 1: Early Stage—tumour confined to the breast (node-negative)
Stage 2: Early disease—tumour spread to movable ipsilateral axillary lymph node (node positive)
Stage 3: Locally advanced disease—tumour spread to the superficial structures of the chest wall, involvement of ipsilateral internal mammary lymph nodes
Stage 4: Advanced (metastatic) disease—metastases present at distant sites such as bone, liver, lungs and brain. Includes supraclavicular lymph node involvement.

The treatment for an **early stage** disease aims to cure, to eradicate the evidence of disease and reduce the risk of recurrence. For the **Locally advanced disease**, the objective is to reduce the tumour mass from inoperable to operable. As a consequence, the neo-adjuvant approach is the preferred one, as it allows an early systemic treatment that targets possible micrometastasis, before the local surgical approach to the primary tumour. In addition, by analysing the surgical specimen one has access to the pathologic results of the chosen systemic treatment. However, the treatment of **metastatic disease** has another goal: to manage disease control, preserving the quality of life.

The main three strategies to treat breast cancer are surgery (that can be conservative or not), radiotherapy, and systemic therapy.
The systemic therapy can be divided in three major groups: chemotherapy, hormonal therapy, and targeted therapy. The usage and sequence differs with the type of tumour and goal of the treatment.
The challenge increases when resistance arises within the patients with metastatic disease and oncologists are left without specific tools to treat a disease whose target is well defined. As an example, for the ER positive breast cancer, the resistance to endocrine therapy is a very important issue. Given that ER positive tumours are hormonal dependent, hormonal therapy is usually the preferred choice. Thus, knowing the causes underlying resistance is immensely important.
The discovery of the relevance of the PI3K-AKT-mTOR pathway in the development of resistance and, consequently, in the selection of targets for its reversion is an important step in this setting.
To be able to treat patients with a hormone-sensitive disease with anti-estrogens therapy and postpone chemotherapy to the most aggressive stages of the disease is undoubtedly a change in the paradigm.

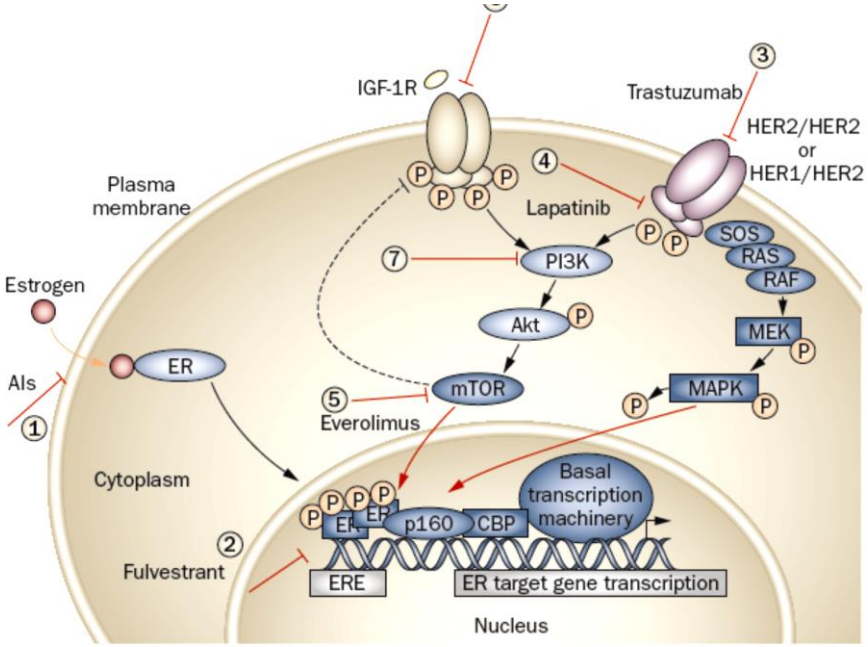


Figure 1 | Targeted therapeutics against HR-positive breast cancer. Each numbered circle represents a therapy option: aromatase inhibitors (**1**); fulvestrant (**2**); monoclonal antibodies against HER1/HER2 receptors (**3**); HER1/HER2 tyrosine kinase inhibitors (**4**); mTOR inhibitors (**5**); monoclonal antibodies against the IGF-1R (**6**); PI3K inhibitors (**7**). Abbreviations: AIs, aromatase inhibitors; CBP, cAMP-response-element-binding-protein-binding protein; ERE, estrogen response element; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase.

Figure 8 : Targeted therapeutics against HR-positive breast cancer. [21]
Each numbered circle represents a therapy option: (1) aromatase inhibitors; (2) fulvestrant; (3) monoclonal antibodies against HER1/HER2 receptors; (4) HER1/HER2 tyrosine kinase inhibitors; (5) mTOR inhibitors; (6) monoclonal antibodies against the IGF-1R; (7) PI3K inhibitors.
Abbreviations: AIs, aromatase inhibitors; CBP, cAMP-response-element-binding-protein-binding protein; ERE, estrogen response element; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase.

2.1.2 Metastatic renal Cell Cancer

Metastatic renal cell cancer (RCC), unlike breast cancer, is a less frequent disease. It constitutes about 3% of all malignant diseases in adults. Its incidence rate has increased worldwide in recent years at a 2% ratio, with about 12,000 related deaths in the USA.

RCC affects twice as many men as women, and occurs more frequently between 40-60 years of age.
The cause for the occurrence of RCC is not known. However, it appears to be linked to some risk factors like tobacco, obesity, family history of renal cancer, diet, and exposure to carcinogenic substances. Von Hippel-Lindau disease, hereditary type 2 papillary RCC and Birt-Hogg-Dubé syndrome are included as genetic factors. [22]

In the USA in 2003, 49% of cases of kidney cancer were diagnosed at stage 1, 10% at stage 2, 13% at stage 3, 18% at stage 4, and the stage was unknown in 10% of cases (2003 data from the National Cancer Data Base, NCDB). The five-year relative survival after kidney cancer in the third version of the Eurocare study, comprising 47,000 kidney cancer cases diagnosed between 1990–1994. [23]

Overall, the 5-year relative kidney cancer survival rate was 56% in males and 58% in females. The prognosis of patients improved at younger ages of diagnosis, with the 5-year relative survival rates falling from 71% for patients diagnosed at 15–44 years old with kidney cancer to 45% for patients diagnosed at 75 years or older. [24]

2.1.3 Pancreatic Neuroendocrine Tumours (pNETs)

Pancreatic neuroendocrine tumours (pNETs) comprise a unique subset of pancreatic tumours. They encompass approximately 1% to 2% of pancreatic tumours, leading to an overall incidence of 1 to 2 cases per 1 million. Autopsy series have reported an incidence of 0.5% to 1.5%.
Pancreatic neuroendocrine tumours also referred to as “islet cell tumours,” occur most commonly as sporadic cases; however, they can be associated with hereditary tumour syndromes such as multiple endocrine neoplasia (MEN) type I and von-Hippel-Lindau disease.
pNETs are mostly well-differentiated tumours, the majority being non-functional, and approximately 40% functional tumours produce bioactive peptides and amines. These are referred to as insulinomas, gastrinomas, glucagonomas, etc., depending on their secreted product. In contrast to other anatomic sites, mitotic rate and

proliferation index play an important role in the WHO characterization of pNETs. Well-differentiated pNETs are generally <2 cm in diameter and exhibit cellular monomorphism, absent or mild nuclear atypia, and low mitotic and proliferative rates.

They are typically confined to the pancreas and lack angioinvasion. Tumours with all of these features but with angio or perineural invasion or increased mitotic activity are at increased risk for malignant behaviour. Strong immunostaining of CgA or peptide hormones is indicative of a well-differentiated pNET, whereas strong a1-antitrypsin immunostaining suggests a solid-pseudopapillary neoplasm. Among functioning well-differentiated pNETs, the type of hormone produced also may be an informative prognostic marker. Tumours producing pancreatic hormones such as insulin, glucagon, somatostatin, and pancreatic polypeptide generally have a lower rate of malignancy compared with tumours producing GI hormones such as gastrin, vasoactive intestinal peptide or neurotensin, or those producing ectopic hormones such as adrenocorticotropic hormone (ACTH), vasopressin or parathyroid hormone. More than 50% of pNETs are nonfunctional and are not associated with a metabolic syndrome. They are, however, histopathologically indistinguishable from functional pNETs. Poorly differentiated pNETs show variable degrees of expression of diffuse neuroendocrine markers, and in situ hybridization for CgA mRNA is a useful diagnostic tool in the evaluation of these tumours. Poorly differentiated pNETs are very rarely associated with a hormonal syndrome, although rare cases of ACTH-producing tumours and tumours associated with hypercalcemia have been reported.

2.1.4 Advanced or Metastatic Melanoma

Melanoma accounts for approximately 5% of skin cancer cases and is one of the deadliest forms of the disease. Malignant melanoma is the 19th most common cancer worldwide, estimated to be responsible for almost 200,000 new cases of cancer in 2008 (more than 1% of the total). Malignant melanoma incidence rates are highest in Australia/New Zealand (where it is the third most common cancer in both males and females, affecting one in nine people - around 11% of the total cases in 2008), and lowest in South-Central Asia. Melanoma has around 200-fold variation in World

incidence rates for males, and 160-fold variation for females. Incidence rates are increasing rapidly in many countries, including in the Nordic countries, where the increase has been attributed to excessive sun exposure during holidays at lower latitudes.

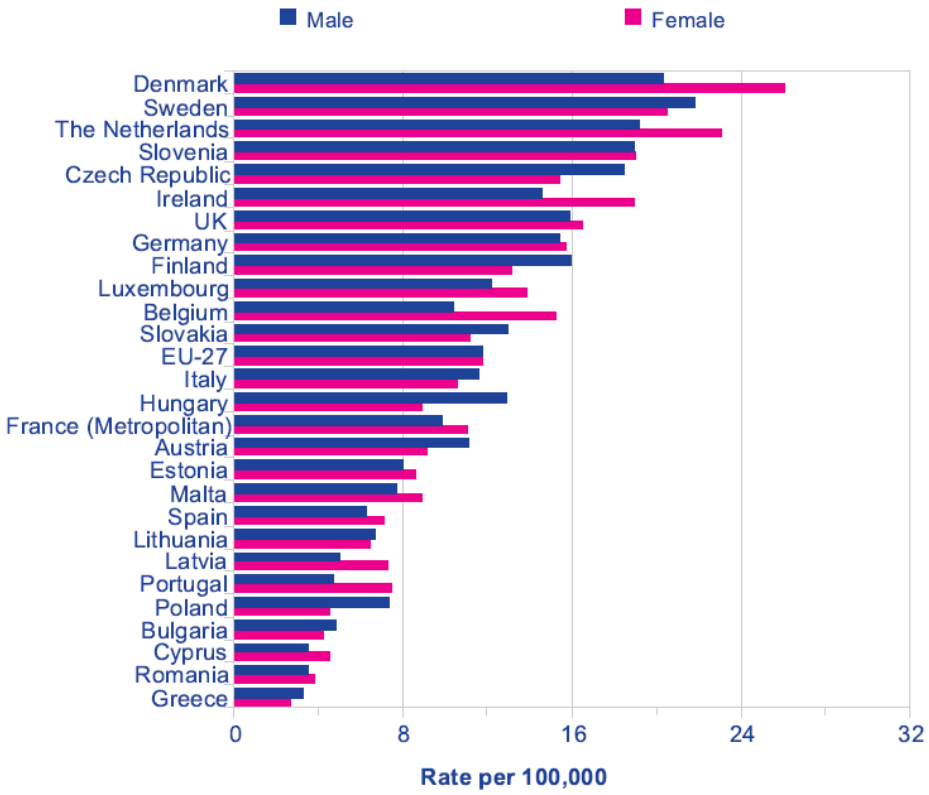


Figure 9: Malignant Melanoma (C43*), European Age-Standardised Incidence Rates, EU-27 Countries, 2008 Estimates

Advanced metastatic melanoma has a 5-year survival rate of less than 10%, and approximately 75% of individuals with an invasive phenotype of melanoma or late-stage melanoma at diagnosis will die from their disease.

For many years, the only systemic therapies for metastatic melanoma were hydroxyurea, interleukin-2, and dacarbazine, none of which produced meaningful outcomes. Last year, the FDA and EMA approved vemurafenib and ipilimumab, two promising but quite disparate drugs that emerged after several years of progress in investigating novel avenues of treatment for advanced or metastatic disease.

Cutaneous melanoma is one of the oncologic diseases where major therapeutic advances were achieved in the last years.

Vemurafenib is an oral inhibitor of BRAF serine-threonine kinase that aims to suppress the constitutive activity of the BRAF protein, which is triggered by one of several mutations in the BRAF gene and leads to tumour cell proliferation. The tumour response produced by Vemurafenib is truly impressive. A total of 78% of patients carrying the BRAF mutation responded, and some patients have maintained a response for as long as 17 months.
Unfortunately, most patients who respond eventually develop resistance to vemurafenib. Two mutually exclusive mechanisms of resistance to vemurafenib have been proposed: reactivation of the mitogen-activated protein kinase (MAPK) pathway resulting from upregulation of NRAS and CRAF; or the activation of alternative survival pathways through upregulation of platelet-derived growth factor receptor-beta (PDGFRβ). Preclinical studies have shown that combining small molecule inhibitors of MEK1/2, phosphatidylinositol 3'-kinase (PI3K), and mammalian target of rapamycin (mTOR) 1/2 consistently triggers apoptosis in cells that have become resistant to BRAF. Several ongoing clinical trials are evaluating the safety and effectiveness of various drug combinations at overcoming BRAF resistance.

Ipilimumab is a fully human monoclonal antibody that targets cytotoxic T lymphocyte antigen-4 (CTLA-4), a checkpoint protein that has inhibitory properties in T-cell regulation. Ipilimumab binds to CTLA-4, thereby deregulating the immune system and allowing antitumor cells to proliferate and preferentially attack the tumour. Ipilimumab has produced complete response in some patients, and extended overall survival. Nevertheless, it is extremely important that the patient has a good performance status, to benefit from the whole treatment.

Vemurafenib and ipilimumab represent significant progresses in improving outcomes for patients with metastatic melanoma, but neither drug is suitable for all patients. Vemurafenib is not effective in patients whose tumours are negative for the BRAF

mutation, whereas those patients with a heavy disease burden need immediate relief and cannot afford to wait for ipilimumab to stimulate an immune response.
In addition, ipilimumab cannot be administered to patients with weak immune systems or those who are immunocompromised.
For patients who are not candidates for therapy with ipilimumab or vemurafenib or whose disease progresses after treatment, clinical trials remain a valuable option. [25]
The clinical investigation in this particular area is very active nowadays, with nearly 394 clinical trials worldwide (Source: clinicaltrials.gov)

The knowledge of the mechanisms of resistance and the pathways that lead to the progression in the treatment of those patients, originated the development of agents such as other checkpoint inhibitors, vaccines, and adoptive immune therapy approaches (which use the patient's immune system to target the tumour as well as novel chemotherapeutic agents and the small molecule inhibitors targeting the RAS/MEK/RAF).

2.1.5 Non-Small cell Lung Cancer

There are 1.6 million people annually diagnosed with lung cancer worldwide. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 85-90% of all lung cancer cases.
There are three types of NSCLC, which vary in cell size, shape and chemical composition:

- Squamous cell carcinoma accounts for 25-30% of lung cancers and is found in the centre of the lung by the air tube
- Adenocarcinoma accounts for 40% of lung cancers and is found in the outer area of the lung
- Large-cell carcinoma accounts for 10-15% of lung cancers and can occur in any part of the lung; tends to grow and spread quickly, making it harder to treat

Approximately 3-8% of patients with NSCLC have the anaplastic lymphoma receptor tyrosine kinase (ALK) gene mutation. ALK is a gene that can fuse with others genes to

form an aberrant "fusion protein" that promotes the development and growth of certain tumours such as anaplastic large cell lymphoma (ALCL), NSCLC, breast and colorectal cancers. There is an unmet treatment need for patients with ALK+ NSCLC once treatment with the only ALK inhibitor available (crizotinib) fails. Patients with ALK+ NSCLC tend to be light or non-smokers and younger than patients without an ALK mutation, with a median age of 54 years. [15]

2.2 Medical Experts Development and Management

KOL relationship management

Identify, develop, and collaborate with current and future KOLs is one of the main objectives of the MSL, and one where collaboration with the sales team is fundamental. An excellent coordination is necessary between professionals that are constantly on the field and the ones who contact more sporadically with HCP. This is one of the main factors for success. Therefore, it was necessary to develop and maintain a national mapping of all hospitals and respective KOLs.

After that mapping, a development plan with specific actions for each of the KOLs was implemented in order to establish strong partnerships and build scientific support, to know what their preferential areas of interest were and understand how the company could help them develop their main projects. These partnership bonds are fundamental to keep these future KOLs truly engaged with us.

ME relationship management

Another fundamental objective is to be able to present and discuss the different areas and developments that are emerging while maintaining a high scientific level. This is not an easy task: it may seem so at first sight, but it requires a high level of preparation, both on knowledge and talk performance. An image of scientific rigor and impartiality is of the utmost importance.

It is thus an absolute imperative to be up-to-date as far as the areas we are working on are concerned. Nowadays, with the improvements in information technologies and

working at a multinational as Novartis, we receive the latest information not only in quantity and quality but also, and not less importantly, at the right moment.
It is often necessary to restrain ourselves from reading all the received information, in search for news or some important result. The strategy I developed to help me was to look at the front page of the communication, and learn where to find the information when I need to prepare for a future meeting.
Establish and maintain ongoing long-term collaborative relationship with KOLs and MEs within their assigned territory.

Disclose scientific information about Novartis Oncology products and therapeutic areas among the main ME. Ensure that an appropriate follow-up is maintained in order to update the most relevant information.
It is thus important to be permanently up-to-date with the information from the company as well as from competitors, so as to be able to maintain a rich and fruitful dialogue with external customers.

Serve as information conduit between the KOLs and the company
One of the benefits of maintaining a professional relationship with the KOLs is that scientific issues and challenges that are important for the company naturally arise, such as an original idea or an IIT proposal.
These ideas might be important to initiate a new research project. It is thus necessary to have a profound knowledge about the areas that are being researched by the company so as to be able to discuss them and help to design new projects. It is also very useful to know who works in which area within the organization in order to obtain the best scientific advice.
Link internal partners to external KOLs for education and research collaboration
A profound knowledge and good relationship with the KOLs allow for an easier and fast contact (KOLs normally have very busy schedules). This way, colleagues from other departments like market access or clinical trials have the opportunity to meet with those experts.

2.3 Clinical Development Support

Being medical affairs field-based personnel, MSLs are very close to the research centres enabling them to provide support to clinical research management teams. New ideas and concepts for ITTs may also arise from research centres.
After the beginning of the trial, the MSL may have a role in collaborating with the recruitment of patients by helping to find potential patients for clinical trials. They are the field based medical personnel, so it might be feasible that in a visit to a ME or KOL a patient profile is discussed and actually recruited for a specific clinical trial. Other task is the report of any anomalous situation with the trial that requires the immediate action from the Clinical Research Associates (CRAs).

2.4 Medical Education and Communication

Medical communication and education are perhaps the most important goals for a MSL. We must be able to provide the most recent and innovative scientific data to our interlocutors. The goal is to provide the audience with the state of the art in terms of scientific publications relative to the compounds and investigation areas we are working on. In order to achieve that, it is very important to be prepared in about every aspect relating to a therapeutic area, whether from our own organization or from the competition. To be well informed about the issues relating to the access to therapeutics or hospital internal processes, both about investigative terms and daily clinical practice, will enrich the dialogue and enable us to be prepared to gather information that might be useful to other members within the organization.
This dialogue may take place in various ways that I will now enumerate:

- In clinical sessions or other forums where it is necessary to develop a new concept or indication, a lecture for medical education actions may be organized, with internal speakers or international KOLs. An example of this new concept is the medical education on GIST. An educational communication with various ME was necessary, from oncologists to gastroenterologists and

anatomo-pathologists, to reach a whole new classification of the disease due to the discovery of a new biomarker and a targeted therapy for the disease.

- One-on-one meetings, where the main data and a summary of the latest and most important communications and publications in a determined area are presented.
- To contribute for the awareness of the company's name as a partner in the scientific communication, academically as well as in research centres.
- Participate in medical activities at congresses and/or Symposia (round tables, workshops, etc.);
- Provide scientific information to HCPs on specific medical inquiries, namely as a response to unsolicited requests for information.
- Provide scientific support to Advisory Boards /Focus Groups related-activities;
- Support to proposals of grants for educational and research initiatives;
- Facilitate investigator interactions with Medical Directors

2.5 Scientific Support

Different aspects are associated with this kind of support: research requested by the ME and a careful selection of the state of the art on the subject, summaries of congresses, guidelines and presentations.
After a careful analysis, I elaborate the most important part and prepare a dossier for the ME or KOL, after the necessary internal approvals.
Other tasks are listed below:

- Maintain clinical, scientific, and technical expertise in specific therapeutic areas; review scientific journals, attend scientific and key technical meetings.
- Represent the Medical Affairs organization in the medical/scientific community
- Respond to and document unsolicited requests for off-label information on our products, including products in development
- Facilitate investigator interactions with Medical Directors

- Implement added value scientific projects, namely epidemiologic studies, registries, preclinical or translational research, multidisciplinary projects involving the education and collaboration of multiple functions in the medical community (e.g. medical specialists, nurses and pharmacists).

2.6 Brand Team Meetings (BTM) Collaboration

A Brand team is actually a cross-functional team. And it can be defined as:

"A cross-functional team is a group of people with different functional expertise working toward a common goal."

Krajewski, L. J. and L. P. Ritzman. 2005[26]

"Cross-functional teams often function as self-directed teams responding to broad, but not specific directives. Decision making within a team may depend on consensus, but often is led by a manager/coach/team leader."

Wikipedia[27]

Business decisions often need the input of people in more than one functional area. This leads to a better understanding of the big picture, allowing people with different ideas, perspectives, and expertise to express their ideas and find creative and innovative solutions to problems that the organization is experiencing. However, combining all of those voices in one cross-functional team creates its own unique set of challenges, requiring specialized team management and leadership skills.
My participation as a MSL in these meetings has evolved with my experience. It started at the same time as my in-job rotation, so the evolution has been simultaneous. In the beginning, my participation was very discrete, listening and trying to understand how these meetings worked and what their objectives were; and also what was expected of my participation in them. So, in the first meetings some tasks were assigned to me, that in some way have shaped my learning curve in this process. In the following meetings, the agenda included themes I proposed and I also gave feedback on my actions.

2.7 Medical Affairs Training and Meetings

To be constantly up-to-date is an important premise in the medical department. In a company such as Novartis that values innovation, compliance and training, this makes even more sense.
So during this period I attended several training courses, congresses and scientific meetings. I will only share in this report the ones that are in the public domain, for company confidentiality reasons.

International Congresses: their purpose is to provide medical education to the most important KOLs and ME, and also to the members of Novartis. They are an excellent opportunity to further develop relationships with the KOLs and ME. By getting to know our interlocutors better, we will increase the probabilities for the establishment of more durable partnerships that are truly mutually beneficial.
At these congresses we can also meet people from the international team with whom it is important to maintain contact. These are usually very busy people that receive a large amount of e-mails. Establishing a connection that will make that person remember your name may be both time-saving and a valuable asset. It is also an extremely important opportunity to promote connections between some national and international KOLs or people from the research area of the organization.
And last but not least, it is an opportunity for scientific update: the latest updates on research and the tendencies for new research areas are presented at international meetings.

National Congresses: the aim of national congresses is to provide the national medical community with the latest scientific information and to report on the state of ongoing national research projects. The company can have a more intervening role by organizing a satellite symposium or have an international speaker invited by us deliver a presentation. The communication between some KOLs and the speakers can also be achieved this way. And ultimately, it is also an excellent opportunity to join the most important ME from a specific area in advisory boards.

In-person training: there are training programmes specifically designed to provide a comprehensive knowledge of the pathologies and products under investigation or already commercialized. So I have attended a few of those programmes and acquired some knowledge of the pathologies, diagnosis, state-of-the-art in management, status of the clinical investigation in that area and who the main competitors are.

Online training: nowadays, with the advances in communication technologies, it is possible to participate in a significant number of training programmes using e-learning. In my opinion, only in some cases, like SOPs or simpler processes, are they truly effective. Training programmes that may raise more doubts or lead to debate should continue to be in-person, or at least have an in-person component .

Self-learning/Study: the self-learning component is extremely important and time-consuming, and it complements all in-presence training programs. Technological advances are both an advantage and a disadvantage for this purpose. We can easily access an endless amount of information nowadays. To know exactly which sites are trustworthy and display high quality information is a fundamental requirement for a high quality study. This task is easier for me because I work in a multinational company that, through its various teams, is able to gather the latest most relevant information and make it available to its associates. [28]

3. Discussion

The MSL concept was created by the American company Upjohn with the drug tolbutamide, designed for the treatment of diabetes mellitus. Basically, the MSL would initiate communication based on medical training and knowledge of the disease, and would create the relationship with physicians. The MSL concept was put into practice in 1967 by a Sales Representative that had a strong interest in scientific data and a great capacity to communicate them.

In spite of having nearly 50 years of existence, the MSL role is still not very clear for many of the stakeholders, at least in countries outside the USA. As MSLs are also

providing support for clinical information of medicines in the market, there may be some confusion as to what the role of an MSL and a Sales Representative is.

At many companies, mainly in the US, field sales representatives are not permitted to speak directly with the MSLs nor can the MSLs share certain information with Marketing. That is not the case in Portugal and in some European countries. In North American countries, this situation is more frequent, due to very strict compliance policies. Because of this communication firewall, companies often struggle with the best way to align Medical and Marketing communication and get the most of what an MSL is, despite continually looking for new ways to reach physicians.

In an ideal situation, where the pressure of sales was not as important and we had unlimited resources available, an MSL would provide support to developing areas, promoting and stimulating clinical research in those areas.

The MSL would thus establish true partnerships with the already known KOLs, through the scientific debate and disclosure of research data.
Additionally, the MSL would carry out the development of "Rising Stars", previously identified by KOLs, providing them with the opportunity to attend top quality medical training in centres of excellence with the leading protagonists of each specific therapeutic area (e.g. Preceptorship programmes). Another important facet of MSL performance is the support to the selection and feasibility analysis of the investigation centres where multicentre clinical trials are to be carried out.

More importantly, the MSL would monitor and be completely up-to-date with scientific news and technologic breakthroughs within the specific therapeutic area.

As a consequence of the drug development, the compound showing effective benefits in clinical trials is then transformed into a product by the marketers. Marketing provides an international designation and a brand, so that a greater number of people may benefit from it. In summary, the MSL is truly paving the way to a successful launch of a determined compound.

This is a reality in US and Canada, as I was able to verify in a training course I attended in Basel, where some senior MSLs shared their experiences and clarified doubts. These MSLs deal exclusively with therapeutic areas where some research is being carried out. For marketed products, the required scientific support is provided by the Medical Advisor.
This means that all the scientific support and communication during clinical investigation are provided by the MSLs. When the final premarketing and marketing stages are reached, their respective teams take the responsibility and the MSL is free to embrace a new project.

In Portugal, from what I have observed, this is far from being a reality; not only for Novartis but also for other companies involved in the area of oncology. We do not have the dimension or the representativeness in Oncology to aspire to a level of resources as Canadian, UK or German teams possess.
The situation is even more difficult due to the highly hostile environment created by the national crisis. Products that take years to be reimbursed and hospitals that take many months to pay their debts do not make our country very attractive for multinationals to invest in very expensive human resources such as those allocated to the medical department. And I do not mean only human resources, but also resources necessary to clinical investigation, that are so important to maintain a sustainable medical department.

Another challenge I came across with that is closely linked to the aforementioned is the interaction between the sales and marketing teams, due precisely to the fact that the difference is not very clear. Again, I verified by the interaction with other MSLs from other countries—even senior MSLs and from countries where the job exists for some time—that this situation is common to all. As always, this is not a generic situation (obviously, not all Sales Representatives nor all Brand Managers are concerned), but an occasional situation that may make the difference between the success and failure of the MSL: especially in areas where the product has already been marketed.

Locally, as I understand it, the key factor for success is a strong and transparent communication. The keyword is to share, share and share.
In a commercial relationship in any industry, established relationships may last many years. This applies even strongly to the pharmaceutical industry, since the product is medicines that have a profound impact in human lives. It is a much more elegant relationship, because this is not a direct sale or purchase. It involves years of sharing, mutual assistance, and communication about the main benefits of products. Many of those relationships began when the medical doctors were still residents, and it was a Sales Representative who helped them with some specific bibliographic research (or book) that was needed at some point of their training. That kind of help or partnerships is very solid and may last for many years.
So it is understandable that if someone else, like the MSL, joins the team and needs to share the time and attention of the same medical doctors, and is even in a privileged position for sharing clinical investigation data, some discomfort may arise. It is thus important to share and communicate with the sales force, so that the sales teams may benefit from the presence of a field-based Medical Affairs person, and so that the MSL has a fast, and now truly privileged access to the main KOLs and MEs.

The challenge is slightly different as far as Marketing is concerned. Here, it is very tempting to impose a more market-oriented communication for the MSL. Throughout the role profile of an MSL is clearly stated that an MSL does not follow Marketing goals. Not that it causes offense or repulsion, since the ultimate aim of the Pharmaceutical Industry is obviously (besides bringing the best therapeutics to the people who really need them) to be profitable.
The objective here is to establish the unbiased communication and to be scientifically driven, not marketing oriented. If the MSL is going to communicate about the same topics as the Sales Representative, it is difficult to mark the difference. This fact may cause some confusion to the KOL or ME and impact the communication flow.
We are addressing the need to delineate boundaries and create some barriers, so that a clear distinction is made as to what is a medical role. Here again we need to use maximum diplomacy, there must be a very clear and assertive communication of

what is beyond our borders. This is a frequent situation that is shared by many MSLs, both national and international. At the end, MSLs need to create and support this fine balance between open cross-functional work and clear non-promotional scientific goals.

Medical affairs departments should establish clear guidance for the role of MSLs within the company. Specifically, MSLs should know how the organization expects them to respond to off-label use inquiries and how to respond to grants, medical education, and investigator-initiated trial grant requests, as well as a variety of other issues. Establishing clear guidance for MSLs can help to ensure that MSLs do not become extensions of the sales department. [18]

Brand Team Meetings (BTM)

This model is used by several companies, either working in small groups composed by representatives of the three key departments (Marketing, Medical and Sales), or in wider groups including members from other departments of the organization like finance, market access and regulatory, for instance. Based on my experience, it is very important to limit meeting agenda, as well as the number of people to include in the meeting. Caution is necessary not to overdo it and end up inviting everybody to every meeting. I think it would be more effective to segment decision-making meetings, which require the presence of board directors, and opinion or creativity meetings, which may include a broader participation even from areas not directly related with Pharmaceutical Industry. Project and action plan follow-up meetings would be composed only by participants who have to intervene in the meeting. In a business unit that deals with several products and BTM, the risk for cross-functional meetings to become impracticable is very high. I consider these meetings a major asset for the organization, but they have to be assertively conducted.

The last challenge that I came across in these last 9 months on the job is the fact that I had the responsibility to contact medical doctors as a National MSL. In spite of being in a small country, two of the most important centers are located more than 200 km away, which does not allow for such a close follow-up as desirable. One way to

overcome that limitation is the participation in national and international meetings, where privileged contacts also occur.

On the positive side, I would like to point out the almost exponential growth of my level of engagement with the company. I have had access to a great deal of information, courses and seminars exclusively conceived for MSLs in this job. The contact with people that perform the job at a European or even global level makes me feel as part of something bigger. It also demonstrates that the company, Novartis, is real and there is a face behind all the guidelines that we receive by e-mail or read on the web-sites. This motivates me to fight for this job, and to fight for this level of involvement with the company's goals to be shared with all our co-workers and clients.
The concepts that have been addressed along this master's programme have also been very useful to me, since they allowed me to tackle more rapidly issues that I was not comfortable with. One of the major advantages of the master's programme, and that I can transpose to my professional life, are the practical exercises that contribute for a much greater agility when dealing with technical situations. We learned how to find reliable answers in the information overflow: in an era where there is so much and so easily accessible information it is vital to recognize valuable information.

After the site selection, the CRAs team will manage all the work related with feasibilities, HA and EC submissions, site initiation visits, screening and monitoring of the study trials. The role of the MSLs, as a field-based medical resource, is to work with the CRAs and support the selection of important investigators and high performing sites. After the investigation phase, all product launch activities will have a strong contribution from the MSL, in a profound teamwork with the Market Access and Marketing department. This contribution makes sense because the MSL is the person that accompanies the development of the product, knowing all the people involved in a specific area, from clinical personnel to pharmacists.
When the product is already established in the market, the MSL will have a very important role in what concerns the use of the product in real life. The report of

adverse effects to Pharmacovigilance and the support to the information of adverse effects management are also activities performed by the MSL.
Parallel to product related activities, there are other activities related to KOLs that concern scientific communication and research projects.
To be constantly up-to-date with all scientific publications and communications on products already commercialized and in research phase is also a very important aspect, and of great responsibility, of a MSL´s job. To know who to contact and where to obtain that information is a major asset that not only maximizes time but also turns the outcome more effective. The participation in international scientific congresses is an excellent tool to reach that objective.
All these activities must comply with the company's code of conduct, even the ones not related with clinical studies, interactions with internal and external groups and replies to unsolicited requests for medical/scientific information.

In my opinion, when the role of the MSL is clearly established, especially as far as the interaction inside and outside the organization is concerned, its contribution in the current climate of austerity is determinant.
Despite the adverse current economic climate, I believe there is an important place in the national pharmaceutical market for the role of MSL.

4. Conclusion

In the present context of financial containment and access restraints, pharmaceutical companies are forced to take a new approach on how to get their message through to the main stakeholders.

In my opinion, the two new emerging functions arising from the present austere climate are Key Accounts Managers (KAMs) and MSLs. KAMs are responsible for negotiations with hospitals and portfolio proposals, and are normally integrated in the Market Access department. MSLs are, as described in this report, the field-based medical personnel.

My experience as an MSL has been both challenging and rewarding. The MSL needs to have the capacity for self-study, to be up-to-date, and to be able to find the relevant information that is fundamental for a good job performance.
A deep knowledge of the pharmaceutical market and of the main stakeholders is of the utmost importance to concentrate efforts and expedite the whole process of selecting and segmenting MEs. This knowledge, together with a previous professional relationship with KOLs and MEs, is an important asset. My past few years of experience in the oncology area has made self-study and market knowledge easier.

Another important aspect of this programme that I would like to point out is the skills I have acquired to perform some tasks. The whole perspective on the development of a drug and its place in the investigation, in the regulating authorities, and in the market were extremely important for my professional development. Learning how to find reliable information was another skill I developed along these two years.

The writing of this report itself has been an excellent exercise of reflection on these nine months, forcing me to make a deep analysis of all the tasks, challenges and benefits I have accomplished.

Due to the fact that the MSL function is relatively new in Portugal and in Novartis Oncology, the interaction of MSLs with the Marketing and Sales departments needs to be adapted and adjusted so that the MSL can be a truly important asset for the company.

It is truly important that the image of the MSL is perceived by other members in the organisation and advocated by the senior managers. MSL image should reflect the value and protection of the company's reputation; and the trust provided by scientifically accurate, fair-balanced, on-label information regarding the safety and efficacy of the products, and off-label information in response to unsolicited questions.

Not only have I learned a great deal from this experience, I also feel that my work has been useful to Novartis because it may be pave the way for communicate best solutions for the right patients.

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